Non-fatal cardiovascular outcome in patients with posttraumatic stress symptoms caused by myocardial infarction

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Abstract: OBJECTIVES: Posttraumatic stress disorder (PTSD) prospectively increases the risk of incident cardiovascular disease (CVD) independent of other risk factors in otherwise healthy individuals. Between 10% and 20% of patients develop PTSD related to the traumatic experience of myocardial infarction (MI). We investigated the hypothesis that PTSD symptoms caused by MI predict adverse cardiovascular outcome. METHODS: We studied 297 patients (61 ± 10 years, 83% men) who self-rated PTSD symptoms attributable to a previous index MI. Non-fatal CVD-related hospital readmissions (i.e. recurrent MI, elective and non-elective intracoronary stenting, bypass surgery, pacemaker implantation, cardiac arrhythmia, cerebrovascular event) were assessed at follow-up. Cox proportional hazard models controlled for demographic factors, coronary heart disease severity, major CVD risk factors, cardiac medication, and mental health treatment. RESULTS: Forty-three patients (14.5%) experienced an adverse event during a mean follow-up of 2.8 years (range 1.3-3.8). A 10 point higher level in the PTSD symptom score (mean 8.8 ± 9.0, range 0-47) revealed a hazard ratio (HR) of 1.42 (95% CI 1.07-1.88) for a CVD-related hospital readmission in the fully adjusted model. A similarly increased risk (HR 1.45, 95% CI 1.07-1.97) emerged for patients with a major or unscheduled CVD-related readmission (i.e. when excluding patients with elective stenting). CONCLUSIONS: Elevated levels of PTSD symptoms caused by MI may adversely impact non-fatal cardiovascular outcome in post-MI patients independent of other important prognostic factors. The possible importance of PTSD symptoms as a novel prognostic psychosocial risk factor in post-MI patients warrants further study.

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Non-Fatal Cardiovascular Outcome in Patients with Posttraumatic Stress Symptoms Caused by Myocardial Infarction

Short title: Posttraumatic stress and cardiovascular prognosis

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ABSTRACT

Objectives: Posttraumatic stress disorder (PTSD) prospectively increases the risk of incident cardiovascular disease (CVD) independent of other risk factors in otherwise healthy individuals. Between 10-20% of patients develop PTSD related to the traumatic experience of MI. We investigated the hypothesis that PTSD symptoms caused by myocardial infarction (MI) predict adverse cardiovascular outcome.

Methods: We studied 297 patients (61±10 years, 83% men) who self-rated PTSD symptoms attributable to a previous index MI. Non-fatal CVD-related hospital readmissions (i.e., recurrent MI, elective and non-elective intracoronary stenting, bypass surgery, pacemaker implantation, cardiac arrhythmia, cerebrovascular event) were assessed at follow-up. Cox proportional hazard models controlled for demographic factors, coronary heart disease severity, major CVD risk factors, cardiac medication, and mental health treatment.

Results: Forty-three patients (14.5%) experienced an adverse event during a mean follow-up of 2.8 years (range 1.3-3.8). A 10 point higher level in the PTSD symptom score (mean 8.8±9.0, range 0-47) revealed a hazard ratio (HR) of 1.42 (95% CI 1.07-1.88) for a CVD-related hospital readmission in the fully adjusted model. A similarly increased risk (HR 1.45, 95% CI 1.07-1.97) emerged for patients with a major or unscheduled CVD-related readmission (i.e., when excluding patients with elective stenting).

Conclusions: Elevated levels of PTSD symptoms caused by MI may adversely impact non-fatal cardiovascular outcome in post-MI patients independent of other important prognostic factors. The possible importance of PTSD symptoms as a novel prognostic psychosocial risk factor in post-MI patients warrants further study.

Keywords: Cardiovascular disease; myocardial infarction; posttraumatic stress disorder; prospective study; psychological stress; risk factor

INTRODUCTION

Between 10 and 20% of patients develop posttraumatic stress disorder (PTSD) in the aftermath of acute myocardial infarction (MI) [1-4]. To meet the diagnostic criteria for PTSD according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [5], patients must have perceived their MI as an event involving threatened death to which they responded with intense fear, helplessness, or horror (criterion A). Three characteristic PTSD symptom clusters (criteria B, C and D) must be present, referring to a) re-experiencing of MI, e.g., in thoughts and dreams, b) avoidance of MI-related stimuli, e.g., intake of cardiac medication, and c) hyperarousal, e.g., irritability and perturbed sleep [1]. These clusters of symptoms must continue for at least one month during which they inflicted clinically significant distress or impairment in daily functioning.

Large scale epidemiologic studies found PTSD caused by different types of trauma increases the risk of incident cardiovascular disease (CVD), even when controlling for sociodemographic factors, major CVD risk factors, and depression [6-8]. In contrast, little is known about the prognostic value of PTSD caused by MI in terms of cardiovascular outcome. One previous study investigated 65 post-MI patients of which 13 qualified for PTSD attributable to MI defined by above-threshold PTSD symptoms (i.e., PTSD caseness) on the Impact of Event Scale [9]. In that study, case definition of PTSD predicted hospital readmissions owing to CVD events, including recurrent MI and unstable angina, at one-year follow-up. Therefore, we performed a prospective study on cardiovascular outcome (i.e., hospital readmissions because of CVD-related events and procedures) in a sizeable sample of patients with a previous index MI who self-rated MI-specific PTSD symptoms at study entry. We hypothesized that elevated levels of PTSD symptoms caused by MI would increase the risk of a non-fatal CVD-related hospital readmission independent of demographic and medical covariates that may also adversely impact the prognosis of CHD.

MATERIALS AND METHODS

Study Participants

The study protocol was approved by the ethics committee of the Canton of Bern, Switzerland. All participants provided written informed consent. The recruitment procedure of post-MI patients has previously been detailed [4]. In brief, we approached consecutive patients referred to the Department of Cardiology, Inselspital, Bern University Hospital, Switzerland, with a verified index ST- and non-ST-elevation MI. All patients underwent a coronary angiography and percutaneous transluminal coronary angioplasty of the culprit lesion. When indicated, percutaneous intervention or bypass surgery was performed in a second step to full revascularization. Further eligibility criteria were living within a 90-min ride from the University Hospital and to speak German sufficiently. Within one year of their index MI, the 383 patients who participated in the present study were sent home the Posttraumatic Diagnostic Scale (PDS; cf. below) to self-rate the level of PTSD symptoms (i.e., posttraumatic stress) caused by the index MI. We decided to assess posttraumatic stress over a variable time course as the DSM-IV distinguishes between several sub-types of PTSD according to a time criterion. Specifically, acute PTSD refers to symptoms which last between one month and less than 3 months, chronic PTSD refers to symptoms lasting 3 months or longer, and delayed-onset PTSD refers to symptoms that begin after an interval of at least 6 months after the trauma [5]. Although repeated assessments of posttraumatic stress would be needed to assure PTSD subtypes, we judged that patient enrolment over one year post-MI might yield a sample in which all subtypes of PTSD symptoms are represented.

For the follow-up, all initially assessed 383 patients were contacted again by mail and asked for their willingness to participate in an investigation that assessed cardiovascular outcome since completion of the PDS. Those who did not respond to the first invitation letter were sent the letter again. Fifty-three (13.8%) of the originally 383 patients were lost to

follow-up, 47 for different reasons (e.g., not responding to the invitation letter, letter returned to sender because of unknown address, no interest) and 6 had deceased during follow-up. We excluded the deceased patients because this group was too small for a meaningful analysis. An additional 33 patients (8.6%) were excluded because we did not have complete data available in terms of CVD risk factors and cardiac medication[1]. This procedure left a final sample of 297 patients with a complete data set for the prospective study presented here. The 86 patients who were either lost to follow-up or had missing data did not significantly differ from these 297 patients in terms of sex, age, PDS score, time sending out PDS after index MI, recurrent MI, and number of diseased coronary vessels (all p-values >0.38).

Assessment of Patient Characteristics

We abstracted sex, age, type of index MI (first-time vs. recurrent MI), the number of diseased coronary vessels, CVD risk factors and cardiac medication from hospital charts which refer to the time of the index MI. Hypertension was defined by a positive history for treatment or systolic and/or diastolic blood pressure ≥140/90 mmHg at rest. Diabetes was defined by a positive history that, if unclear, was verified by one-time glucose level >200 mg/dL. The status of current smoking (yes/no) was also obtained from the charts. The use (yes/no) of aspirin, statins, beta blockers, and ACE inhibitors was also noted.

Assessment of Posttraumatic Stress Symptoms

We used the validated German version of the Posttraumatic Diagnostic Scale (PDS) which is a self-report measure comprising 17 questions mapping onto DSM-IV symptoms for PTSD [11,12]. There was good internal consistency in our sample of post-MI patients for the

[1] When these missing values were imputed according to the procedures described by Schafer [10], posttraumatic stress was also significantly predictive of CVD-related hospital readmissions controlling for covariates (50 adverse events occurred during follow-up in the 330 patients of whom 33 had some imputed data points).

total PDS score (Cronbach's α =.91) and the 3 PTSD symptom cluster scores (criteria B, C, and D) of re-experiencing (α=.88), avoidance/numbing (α=.80), and hyperarousal (α=.76). In the questionnaire we replaced the term "event" with the term "heart attack" [2]. Patients rated on a 4-point scale how often they had experienced each symptom during the past month (0=not at all, 3=often) yielding a PTSD symptom severity score between 0-51 (re-experiencing: 0-15, avoidance: 0-21, hyperarousal: 0-15). Missing items were replaced with the mean of completed items of the respective symptom cluster. Table 1 summarizes the 17 items of the PDS according to symptom clusters B-D of PTSD [11]. The PDS performs well as a screening tool to identify clinical cases of PTSD [13]. A total PDS score ≥18 recently yielded the best balance between sensitivity and specificity for screening for PTSD (i.e., PTSD caseness) across different samples of trauma survivors (area under the ROC curve 0.90-0.96) [14].

The PDS does not assess the DSM-IV criterion A2 for PTSD, i.e. to what extent the patients responded to the A1 event (i.e., the MI) with "intense fear, helplessness, or horror". Therefore, at the time when they completed the PDS, we asked the patients to retrospectively rate on a numeric scale "fear of dying" and "feelings of helplessness" they had perceived during MI. Specific items were (0 = absolutely not true, 10 = absolutely true) [2]: "During my referral to the hospital, the emergency unit, or the intensive care unit, I was afraid I was dying." and "When the doctor told me I had a heart attack, I was frightened, felt helpless, and was afraid of losing control over the situation."

Assessment at Follow-up

The follow-up period referred to the time interval between sending out the PDS to assess PTSD symptoms in relation to the index MI and a semi-structured telephone interview by using a standard protocol. During the interview patients were asked whether they had been

hospitalized because of a new CVD event or CVD-related intervention. We assessed the following specific diagnostic categories and interventions by using a checklist (yes/no answers): recurrent MI, elective and non-elective intracoronary stenting, coronary artery bypass surgery, pacemaker implantation, cardiac arrhythmia, cardiac arrest, cerebrovascular insult, transient ischemic attack, hypertensive crisis, and chronic heart failure. If patients' self-report about the cardiovascular cause for hospitalization was non-specific, their primary care physicians were contacted by telephone to verify the type of CVD-related event or intervention (all contacted physicians could be reached). We did not consider "angina pectoris" as a diagnostic category because chest pain has many cardiac and non-cardiac causes, one being psychological distress that is particularly high in traumatized subjects. However, recurrence of chest pain previously predicted posttraumatic stress in patients 12 months after hospital admission for an acute coronary syndrome [15]. We thus asked about chest pain which had occurred since index MI having prompted patients to see a doctor but remained unexplained. We further asked patients whether they had received mental health treatment in the form of antidepressant medication and/or psychotherapy since the index MI.

Statistical Analysis

Data were analyzed using SPSS 15.0 statistical software package (SPSS Inc. Chicago, IL) with a significance level of $p<0.05$ (two-tailed). For calculations of differences between groups, Student's *t* test, Pearson chi-square test, and Fisher's exact test were used where appropriate. We ran Cox proportional hazard models to estimate the predictive value of posttraumatic stress severity (assessed by the PDS at study entry) for the relative risk of a hospital readmission during follow-up because of a CVD event or CVD-related intervention (combined endpoint). For this analysis we used the total PDS score as a continuous variable (i.e., the PDS cut-off ≥18 was only used to compute the prevalence of PTSD caseness and to

compare characteristics between patients with high versus low PDS scores). Total PDS scores showed a skewed distribution towards small values. Although not normally distributed predictor variables have generally no impact on regression-type models [16], we reran all models with normally distributed square root transformed total PDS scores; this procedure did not change the significance of posttraumatic stress as a predictor of CVD-related outcome (data not shown). Because a one point higher level on PDS scores predicts a change in the relative risk[2] that, even when being statistically significant, is unlikely of clinical relevance, we expressed the change in the hazard ratio (HR) with 95% confidence interval (CI) for a 10 point higher level on the total PDS score and for a 3 point higher level on the individual PTSD symptom scores. For this purpose total PDS scores and individual PTSD symptom scores were divided by 10 and 3, respectively, prior to entering them into the models.

Control variables that might potentially affect CHD outcome were defined *a priori,* whereby sex and age (demographic factors) were treated as control variables in all models. To prevent over-fitted models given the number of endpoint events [16], we first identified potentially relevant predictors of outcome. Together with sex and age, these were grouped into five separate blocks of covariates: 1) CHD severity: type of the index MI (first-time vs. recurrent MI), number (1, 2, or 3) of diseased coronary vessels); 2) major CVD risk factors: hypertension, diabetes, current smoking (all coded as yes/no); 3) cardiac medication prescribed at hospital discharge: aspirin, statins, beta blockers, ACE inhibitors (all coded as yes/no); 4) unexplained chest pain since index MI (coded as yes/no); and 5) mental health treatment since index MI: antidepressant medication, psychotherapy (both coded as yes/no). Control variables emerging as outcome predictors ($p<0.10$) from these five blocks were entered into the final model together with sex, age, and posttraumatic stress (one block).

[2] The term "relative risk" refers to the hazard ratio throughout the manuscript.

RESULTS

Patient Characteristics

The mean±SD time since index MI the PDS was sent was 76±59 days (range 12-365); to 278 patients (93.6%) the PDS was sent between 1 and 6 months post-MI. Across all 297 post-MI patients, total PDS score was 8.8±9.0 (range 0-47), fear of dying score was 2.8±3.2 (range 0-10), and helplessness score was 3.0±3.2 (range 0-10). Total PTSD symptoms correlated with fear of dying ($r=0.57$, $p<0.001$) and helplessness ($r=0.65$, $p<0.001$) suggesting that, in agreement with the DSM-IV criterion A of PTSD, patients with greater posttraumatic stress responded to the MI with more intense fear, helplessness, or horror [5]. Most frequently reported PTSD-specific symptoms of re-experiencing MI-related events (range 0-3) were intrusive images about MI (0.82±0.88) and emotional upset when reminded of MI (0.75±0.87); reliving of MI (0.44±0.71), physical reactions when reminded of MI (0.41±0.76), and nightmares about MI (0.29±0.66) were comparably less often named.

Forty-five patients (15.2%) met case definition criteria for PTSD according to a PDS score ≥18 [13]. Table 2 shows the characteristics of patients according to high (PDS score ≥18) versus low (PDS score <18) levels of PTSD symptoms. Compared to patients with low levels of PTSD symptoms, those with high levels reported greater fear of dying and helplessness, were more often female and younger, but had less severe CHD with regard to the number of diseased coronary vessels. Other major CVD risk factors and prescription of cardiac medications did not differ between groups. During follow-up, patients fulfilling PTSD criteria were more likely to have received mental health treatment than patients not fulfilling PTSD criteria.

Adverse Cardiovascular Events During Follow-up

The mean duration of follow-up was 2.8 years (range 1.3-3.8) during which a CVD-related hospital readmission occurred in 43 (14.5%) of the 297 post-MI patients who were available for follow-up. The 43 CVD-related events or interventions were 10 (3.4%) recurrent MIs, 13 (4.4%) non-elective stents, 11 (3.7%) elective stents, 4 (1.3%) coronary artery bypass surgeries, 1 (0.3%) pacemaker implantation, 1 (0.3%) cardiac arrhythmia, and 3 (1.0%) cerebrovascular events. There were no hospital readmissions because of cardiac arrest, hypertensive crisis, or chronic heart failure.

PTSD Symptoms and CVD-related Hospital Readmissions

Table 3 shows that for a 10 point higher level in the PDS score, there was a 45% to 51% higher relative risk of a CVD-related hospital readmission with adjustments for the five blocks of covariates. From these blocks of covariates, hypertension status (HR 2.51, 95% CI 1.19-5.31) emerged as the only independent predictor of the outcome. The final model showed a 42% higher relative risk of a CVD-related hospital readmission with a 10 point higher level in posttraumatic stress controlled for sex, age, and hypertension. Figure 1 illustrates survival curves across quartiles of continuous PTSD scores. In terms of individual PTSD symptom scores, there emerged a 29% higher relative risk of a CVD-related hospital readmission for a 3 point higher level in re-experiencing symptoms, controlling for sex, age, and hypertension (HR 1.29, 95% CI 1.01-1.65). Similar risks were revealed for a 3-point higher level in symptoms of avoidance (HR 1.27, 95% CI 1.04-1.55) and of hyperarousal (HR 1.33, 95% CI 1.03-1.71).

Table 3 shows a complementary analysis for which we only considered major and unscheduled CVD-related hospital readmissions. In other words, we excluded the 11 patients

who underwent elective stenting during follow-up. Hypertension status was the only independent predictor of outcome (HR 3.77, 95% CI 1.43-9.97). In the fully adjusted model, the relative risk for an adverse event was 45% for a 10 point higher level in the PDS score. The relative risk of an adverse event was 39%, 27%, and 33%, respectively, for a 3 point higher level in symptom scores of reexperiencing (HR 1.39, 95% CI 1.07-1.80), avoidance (HR 1.27, 95% CI 1.02-1.58), and hyperarousal (HR 1.33, 95% CI 1.00-1.76).

Sensitivity Analyses

To test for the robustness of the above findings we performed five sensitivity analyses. We restrict the presentation of the results to the fully adjusted models, which controlled for sex, age, and hypertension status. All HRs refer to the increase in the relative risk of a CVD-related hospital readmission for a 10-point higher level in the total PDS score for the respective subsample.

First analysis: We controlled for the time between index MI and sending out the PDS to account for the possibility that longer duration of PTSD symptoms affects CVD outcome: HR 1.44, 95% CI 1.08-1.91 (n=297; 45 with high PTSD symptom levels; 43 events).

Second analysis: We excluded 21 patients (7.1%) who were sent the PDS earlier than 30 days (i.e., between 12 and 29 days) after the index MI to consider only those participants who clearly fulfilled the time criterion for PTSD (i.e., symptom duration of at least one month): HR 1.45, 95% CI 1.08-1.94 (n=276, 45 with high PTSD symptom levels; 39 events).

Third analysis: We excluded 19 patients (6.4%) who were sent the PDS more than half a year after their index MI (i.e., between 182 and 365 days) to account for the skewed distribution of this time interval: HR 1.46, 95% CI 1.08-1.98 (n=278, 41 with high PTSD symptom levels; 40 events).

Fourth analysis: We excluded 3 patients (1.0%) who indicated a CVD-related hospital readmission in the same month in which they also completed the PDS to account for the possibility that the event unduly affected the PDS score: HR 1.45, 95% CI 1.08-1.94 (n=294, 45 with high PTSD symptom levels; 40 events).

Fifth analysis: We excluded the 33 patients with antidepressant medication to test whether the association of posttraumatic stress with CVD-related hospital readmissions was independent of this surrogate of depressive symptoms: HR of 1.41, 95% CI 1.02-1.95 (n=264; 33 with high PTSD symptom levels; 37 events).

DISCUSSION

We found that elevated levels of PTSD symptoms caused by MI predicted the risk of future hospital readmissions due to a combined endpoint of non-fatal CVD events and CVD-related interventions over a mean follow-up period of almost three years. This relationship was independent of several other potential predictors of adverse outcome. Results from five sensitivity analyses suggested the predictive value of posttraumatic stress for future non-fatal CVD-related hospital readmissions is robust. We further found that PTSD symptoms predicted poor cardiovascular outcome even when elective intracoronary stenting was not considered as an outcome. This may suggest that including elective stenting in our combined outcome did not dilute the "true" time interval after which hospital readmission became inevitable due to the progression of CHD.

Our findings suggest that the risk of adverse CVD-related outcome of post-MI patients lies along a continuum of PTSD symptom severity. Specifically, in the final multivariate-adjusted primary analysis, a 10 point higher level in the PDS score showed an increase of 42% in the relative risk for a CVD-related event. Moreover, 15.2% of MI survivors met a PDS cut-off score ≥18 which previously performed well as a screening tool

for PTSD caseness in individuals with non-MI related traumas [14]. This prevalence of PTSD caseness largely concurs with that found in other samples of post-MI patients investigated in the first year after MI [1], but it is several times higher than the 12-month prevalence of PTSD in a representative Swiss population sample [17].

Because PTSD caused by MI is frequent and clinically important, clinicians may want to routinely assess PTSD symptomatology in their post-MI patients, even though it is currently unknown which treatment should be delivered and whether it may alleviate cardiovascular morbidity. We found that patients meeting PTSD caseness criteria were younger and seemed to have less severe CHD than non-PTSD cases. Hence it might be that the relatively younger post-MI patients with PTSD, but not necessarily those with more severe CHD, particularly benefit from PTSD treatment. One small study showed a decrease in MI-caused PTSD symptoms and CVD risk factor status after trauma-focused cognitive behavior therapy (CBT) plus education compared to education alone [18]. This finding is in line with the established knowledge that the most effective psychotherapies for PTSD are those focusing on the psychological trauma [19]. Importantly, trauma-focused CBT seems safe in patients with PTSD resulting from cardiovascular illness (incl. MI) since hemodynamic activity does not evidently increase during imaginal exposure therapy [20]. In addition, selective serotonin reuptake inhibitors (SSRIs) in sufficiently high doses are first-line drugs to treat PTSD [21] and SSRIs (but not tricyclic antidepressants, TCAs) are also safely administered to patients with CHD [22]. Interestingly enough, adjustments for psychotherapy and antidepressant medication did not reduce the risk of adverse outcome in relation to PTSD symptoms in our patients. It might be that traumatic experience of MI was not specifically addressed in those psychotherapies and that the dosage of antidepressants was too low to alleviate posttraumatic stress. However, it should also be noted that we did not have information about the type of prescribed antidepressants. Therefore, we cannot exclude

the possibility that favourable effects of SSRIs on cardiovascular outcomes were outweighed by unfavourable effects of TCAs such that the overall effect of antidepressants was null.

Atherosclerotic mechanisms underlie the vast majority of CVD events and CVD-related procedures that were considered as outcomes in our study. Although not investigated here, several pathophysiologic mechanisms might explain the atherosclerotic CVD risk associated with PTSD symptoms. These may particularly include low-grade systemic inflammation [1]. Neuroendocrine and autonomic alterations in PTSD are thought to mediate a dysfunctional peripheral stress response involving a range of immunological changes with the associated wear and tear to the body giving rise to the clinical manifestation of CVD and atherothrombotic events [23,24]. There is particular evidence for altered hypothalamic-pituitary adrenal axis function involving peripheral hypocortisolemia and a hyperadrenergic state in PTSD [25,26]. Plasma levels of cortisol were lower and those of the proinflammatory cytokine interleukin-6 were higher in patients with PTSD caused by MI than in post-MI patients with no PTSD [27,28]. Another study found a positive correlation between plasma norepinephrine and interleukin-6 levels in PTSD related to combat exposure [29]. Patients with PTSD may also have decreased vagal activity [30]. Vagal withdrawal might give rise to enhanced production of proinflammatory cytokines by tissue macrophages [31], thereby potentially kindling inflammation in coronary arteries [32].

We mention several limitations of our study. The link between PTSD and poor prognosis of CHD might also be mediated by low adherence to cardiac therapy [33] and adverse life style such as smoking, excessive alcohol consumption, low physical activity, and dietary habits promoting dyslipidemia and overweight [1]. We controlled for current smoking and statin use as a proxy measure of hyperlipidemia, but we had no information available about adherence, physical activity, diet, and body mass index to control for obesity. However, obesity has also been shown to be associated with reduced mortality after ST-elevation MI

[34] in which case the controlling for obesity should have theoretically strengthened the predictive value of posttraumatic stress for CVD-related hospital readmissions. It would have further strengthened our study if we had also taken into account as covariates important prognostic factors like cholesterol levels, prevalence of pre-infarction angina, Killip class, left ventricular function, and peak levels for cardiac enzymes. The window for sending the questionnaire was one year such that we cannot fully rule out that some cases of PSTD that resolved before the assessment was made. It is also possible that more severe and prolonged chest pain before MI and between MI and PTSD assessment had contributed to the level of posttraumatic stress [15]. However, we adjusted for CHD severity, unexplained chest pain since index MI, and the time interval between index MI and PTSD assessment; moreover, the prevalence of PTSD did previously not decrease with longer time elapsed within the first year since MI [1]. We did not assess other psychosocial risk indicators for post-MI prognosis such as low social support [35] and depression [36] both of which are also associated with PTSD in cardiac patients [15,37]. However, PTSD symptoms previously predicted incident CVD independent of depression [6-8] and some authors argue that separating out depression as a distinct disorder when it occurs with PTSD more than one year after trauma is an arbitrary distinction [38]. Moreover, we found that PTSD specific symptoms of reexperiencing MI-related cues were individually predictive of poor CVD-related outcome. Antidepressant medication (i.e., a surrogate of clinical depression) was not a significant predictor of outcome and dropping patients with antidepressant medications also maintained the predictive value of posttraumatic stress. Although avoidance and hyperarousal symptoms, which are less specific to PTSD, were also individually predictive of adverse outcome, our findings suggest that components unique to PTSD added to poor post-MI prognosis above and beyond aspects related to depression.

We conclude that elevated levels of PTSD symptoms caused by MI may increase the risk of future cardiovascular readmissions in post-MI patients suggesting that PTSD caused by MI is an important clinical entity. Randomized controlled trials seem warranted to investigate which interventions effectively reduce PTSD symptoms caused by MI and whether such interventions ultimately improve cardiovascular outcome in post-MI patients.

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Table 1. The 17-Item Posttraumatic Diagnostic Scale Asking About Index MI as the Traumatic Event

PTSD symptom cluster B: Re-experiencing MI as a traumatic event
1. Intrusive images about MI
2. Nightmares about MI
3. Reliving of MI
4. Emotionally upset when reminded of MI
5. Physical reactions when reminded of MI
PTSD symptom cluster C: Avoidance of MI as a traumatic event and psychic numbing
6. Trying not to think, talk, or have feelings about MI
7. Trying to avoid activities, places, or people that remind of MI
8. Memory loss for important aspects of MI
9. Loss of interest in previously enjoyed activities
10. Feeling distant or cut off from other people
11. Feeling emotionally numb
12. Sense of a foreshortened future
PTSD symptom cluster D: Hyperarousal
13. Sleeping difficulties
14. Irritability or outbursts of anger
15. Difficulty concentrating or completing tasks
16. Hypervigilance
17. Exaggerated startle response

MI, myocardial infarction; PTSD, posttraumatic stress disorder

Table 2. Characteristics of 297 Patients per PTSD Symptom Level

Variable	High PDS score (n=45)	Low PDS score (n=252)	*P*-value
Total PTSD symptoms (score)	25.9 ±7.4	5.8 ± 4.9	<0.001
Re-experiencing symptoms (score)	8.3 ± 3.5	1.7 ± 1.9	<0.001
Avoidance symptoms (score)	10.3 ± 3.5	2.0 ± 2.1	<0.001
Hyperarousal symptoms (score)	7.3 ± 3.4	2.0 ± 2.1	<0.001
Fear of dying during MI (score)	6.1 ± 3.1	2.3 ± 2.8	<0.001
Feelings of helplessness during MI (score)	6.8 ± 2.5	2.3 ± 2.8	<0.001
Women (%)	28.9	15.1	0.031
Age (years)	55.7 ± 7.6	61.7 ± 10.7	<0.001
Time since index MI PDS was sent (days)	83.9 ± 59.4	74.2 ± 59.1	0.331
Recurrent MI (%)	8.9	9.1	1.000
1-, 2-, 3-vessel disease (%)	64, 27, 9	41, 32, 27	0.006
Hypertension (%)	64.4	61.5	0.742
Diabetes (%)	17.8	11.5	0.229
Current smoker (%)	51.1	38.1	0.101
Aspirin (%)	100	98.4	1.000
Statin (%)	100	96.4	0.364
Beta blocker (%)	97.8	91.3	0.222
Angiotensin converting enzyme inhibitor (%)	60.0	70.6	0.155
Chest pain since index MI (%)	4.4	3.2	0.652
Antidepressant therapy since index MI (%)	26.7	8.3	0.001
Psychotherapy since index MI (%)	17.8	6.7	0.035

PDS, Posttraumatic Diagnostic Scale; PTSD, posttraumatic stress disorder; MI, myocardial infarction

Table 3. Multivariate Relative Risk for Future Adverse Cardiovascular Events for a 10 Point Higher Level in the Posttraumatic Diagnostic Scale Score (Hazard Ratio, 95% CI)

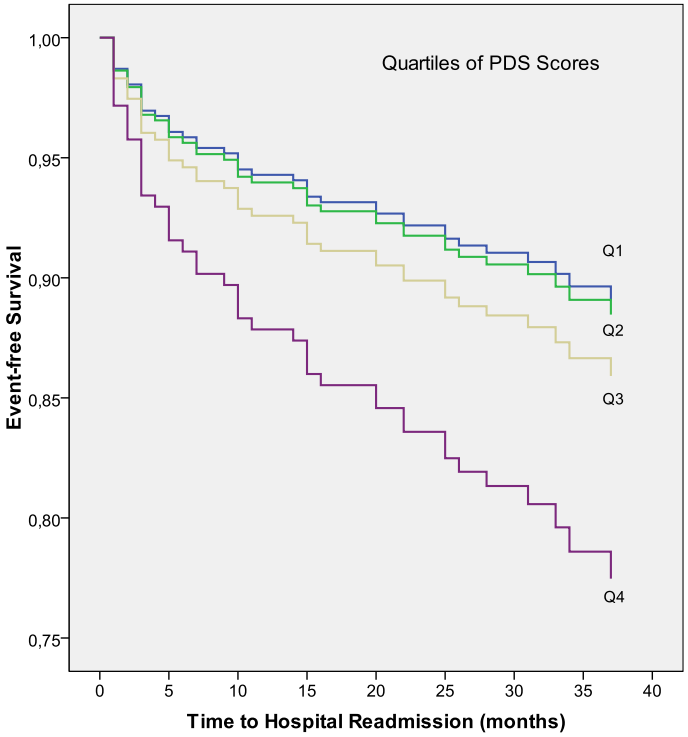
Control Variables [1)]	*CVD-related readmissions (n=297, 43 events)*	*CVD-related readmissions without elective stents (n=286, 32 events)*
CHD severity	1.50 (1.13-1.98)	1.56 (1.15-2.12)
CVD risk factors	1.51 (1.12-2.03)	1.57 (1.13-2.18)
Cardiac medication	1.45 (1.09-1.93)	1.48 (1.09-2.02)
Unexplained chest pain	1.45 (1.10-1.92)	1.51 (1.11-2.04)
Mental health treatment	1.46 (1.10-1.95)	1.54 (1.13-2.09)
Final model		
Female sex	0.42 (0.15-1.18)	0.28 (0.07-1.16)
Age	1.01 (0.98-1.04)	1.00 (0.96-1.04)
Hypertension	2.34 (1.12-4.90)	3.47 (1.33-9.06)
Posttraumatic stress	1.42 (1.07-1.88)	1.45 (1.07-1.97)

[1)] All models controlled *a priori* for sex and age. Additional predictors ($p<0.10$) to be included in the final model were tested in five separate blocks. *Coronary heart disease (CHD) severity:* number of diseased coronary vessels, recurrent myocardial infarction. *Cardiovascular disease (CVD) risk factors:* hypertension, diabetes, current smoking. *Cardiac medication:* statin, aspirin, beta blocker, angiotensin-converting enzyme inhibitor. *Unexplained chest pain:* had occurred since index MI and prompted physician visit. *Mental health treatment:* antidepressant medication, psychotherapy. *Final model:* all four variables were entered in one block (female sex and positive history of hypertension both coded as "1")

Legend to Figure 1

Survival function for quartiles (Q) of posttraumatic stress symptom severity rated by the Posttraumatic Diagnostic Scale (PDS). PDS scores were 0.7±0.8 for Q1 (n=68, 9 events), 3.9±0.8 for Q2 (n=56, 7 events), 8.6±2.3 for Q3 (n=72, 12 events), and 21.8±7.8 for Q4 (n=58, 15 events). Adjustment was made for sex, age, and hypertension.

Figure 1


Quartiles of PDS Scores
Q1
Q2
Q3
Q4
Event-free Survival
1,00
0,95
0,90
0,85
0,80
0,75
0
5
10
15
20
25
30
35
40
Time to Hospital Readmission (months)